REMARKS

First, Applicants would like to thank Examiners Schultz and Examiner McCabe for their time and courtesy during interview with Applicants Donegan and Engelhardt and Applicants' representatives, Ronald C. Fedus and Cheryl H. Agris on April 29, 2004. During the interview, the rejections under 35 U.S.C. 112 (written description and enablement) and the prior art rejections were discussed. Issues discussed during the interview will be further discussed in this response.

Applicants herewith submit a Sequence Listing. Additionally, the specification has been amended to insert SEQ ID Nos.

Claims 245-323 are pending in the above-referenced application. Furthermore, as will be discussed in further detail below and in view of discussions during the interview on April 29, 2004, claims 245, 248, 249, 251, 254, 255, 256, 264, 265, 268, 272, 290, 299, 303, 304-313, 318, 321 have been amended to more distinctly claim that which Applicants regard as their invention. Claims 246-247, 257-259, 261, 263, 266-267, 269, 271, 273-283, 314-316 have been cancelled without prejudice. The claim amendments are supported by the specification.

1. Restriction of Claims 318-323

It is asserted that newly submitted claims 318-323 are directed to an invention that is independent or distinct from the invention originally claimed. In the Examiner's view, the two new methods are drawn to a process of introducing nucleic acid products of claims 245 or 299 into a cell and are thus related to the products of claims 245 and 299 as product and process of use.

Applicants respectfully traverse. In Applicants view, independent claims 318 and 321 are "linking" claims. A linking claim in MPEP §809.03 is defined as follows:

> There are a number of situations which arise in which an application has claims to two or more properly divisible inventions, so that a requirement to restrict the application to one would be proper, but presented in the same case are one or more claims (generally called "linking" claims) inseparable therefrom and thus linking together the inventions otherwise divisible.
>
> The most common types of linking claims that, if allowed, act to prevent restriction between inventions that can otherwise be shown to be divisible, are genus claims linking species claims;
>
> (B) a claim to the necessary process of making a product linking proper process and product claims;
>
> (C) a claim to "means" for practicing a process linking proper apparatus and process claims; and
>
> (D) a claim to the product linking a process of making and a use (process of using)

According to MPEP §809:

> The linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn. Any claim directed to the nonelected invention(s) previously withdrawn from consideration, which depends from or includes all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability. Where such withdrawn claims have been canceled by applicant pursuant to the restriction requirement, upon the allowance of the linking claim(s), the examiner must notify applicant that any canceled, nonelected claim(s) which depends from or includes all the limitations of the allowable linking claim may be reinstated by submitting the claim(s) in an amendment. Upon entry of the amendment, the amended claim(s) will be fully examined for patentability.

Clearly, claims 318 and 321 constitute linking claims since each of these claims link the products recited in claims 245 and 299 respectively with processes of using this product.

Additionally, the Examiner has required restriction between product and process claims. However, Applicants note that according to MPEP §821.04, where Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined.

2. The Rejections Under 35 U.S.C. §112-Written Description

Claims 245, 247-260, 262-265, 268, 270-274, 279, 280, 282-284, 286-290, 292, 296-317 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In the Examiner's view, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, it is stated

> Regarding the use of terms such as a primary acid construct, a production center, propagation, production, and inherent cell systems, these terms are considered to have open, non-limiting definitions in the specification due to the for example type language, and as such are read broadly. Claims incorporating these terms would need to be supported by a sample commensurate with such breadth. This is considered to comprise a vast number of species, as in the case of inherent cell systems or production. As stated in the previous Office action, in order to be in possession of such breadth, applicant would need to disclose a representation number of species, the sum of which provides one of skill in the art with the knowledge to

> immediately envisage the genus. The claims containing the language above are extremely broad, encompassing virtually any living being capable of being infected by a virus, from bacteria, to humans, and as such, the specification simply does not provide an adequate number of representation species to possess such breadth.

Applicants respectfully traverse the rejection. However, as discussed during the interview and as noted above, 245, 248, 249, 251, 254, 255, 256, 264, 265, 268, 272, 290, 299, 303, 304-313, 318, 321 have been amended to more distinctly claim that which Applicants regard as their invention and to advance prosecution. Specifically, amended claim 245 is directed to a composition comprising **a primary nucleic acid,** which upon introduction into a eukaryotic cell produces **a secondary nucleic acid** which produces a **gene product** and/or **a tertiary nucleic acid,** with the proviso that the primary nucleic acid is not obtained with the second or tertiary nucleic acid or gene product. Amended claim 265 is directed to a composition comprising **a nucleic acid** which produces **in a eukaryotic cell** a **gene product** comprising (i) a nuclear localization sequence comprising a portion of snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA and a reimportation signal and (ii) **an antisense of sense nucleic acid.** Claim 290 has been amended to be directed to a method for localizing a **gene product**. Amended claim 299 is directed to a **nucleic acid** which upon introduction into a eukaryotic cell produces more than one specific **nucleic acid**, where each specific **nucleic acid** produced is substantially nonhomologous with each other and is complementary with a specific portion of one or more **mRNA targets** in a **eukaryotic cell** or binds to a specific protein in said **eukaryotic cell**.

It is Applicants' position that the specification has provided a sufficient number of representative samples to support the currently pending claims.

Applicants, for Examiner's reference has provided the table below showing support in the specification and figures for the currently pending claims.

Claims	**Support in spec.**	**Support in Figures**
Claims 245, 248-256, 260, 262, 264, 3: composition comprising 1° nucleic acid which produces a 2° or 3° nucleic acid and cells containing composition (262) and 2° or 3° nucleic acid (264)	pp. 91-92 (definitions of "1° nucleic acid construct", "Production center", "propagation", "production", "inherent cell system" pp. 92-100- description of constructs Examples 21-25, pp. 157-162	34-40
Claims 265, 268, 270, 272, 284, 286-290, 296-298-composition comprising a nucleic acid product that produces a product comprising a localization signal and sense or antisense nucleic acid sequence and method for localizing nucleic acid product	pp. 101-104 and ex. 26 (pp. 162-164)	43, 44
Claims 299, 303-313, 321-323- nucleic acid component **produces** more than one specific nucleic acid sequence when introduced into a **eukaryotic** cell, each such specific sequence so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more single-stranded nucleic acid of interest in a cell or **binds** to a specific protein of interest in a cell.	pp.104-110 (section 7-multicassettes); ex. 27, 28, 29 (pp. 164-167	45, 46, 47

For the sake of completeness, Applicants would also like to respond to the following assertion made in the Office Action.

> Applicants take issue with the assertion made in the Office Action that is it necessary to provide the chemical structure of the claimed nucleic acid constructs or components. At the outset, this is not believed to have been asserted in the previous Office action. If applicants disagree, applicants are requested to point out specifically where such a demand has been made. Again at issue is whether the description provided by applicants would allow one of skill to envision the entire breadth of the claimed genus. The language recited in the claims are so broad as to encompass not only the species disclosed by applicants, but also include virtually any living being that contains or makes RNA, such as a human, bacterium, or ribozyme as found in claim 245. This is a broad genus indeed. Applicants are not considered to have described an adequate number of species to envision the genus as claimed.

In response, Applicants respectfully point out that in the previous Office Action issued by Examiner M. Schmidt, the requirement of reciting the chemical structure of the claimed nucleic acid construct is stated on page 15. Furthermore, Applicants note that the currently pending claims are directed to compositions expressed in **eukaryotic cells**. Again, as noted above, Applicants assert that an adequate number of species have been described.

Finally, it is asserted that "applicants have not exemplified compounds that work *in vivo,* and moreover, have not taught with it is about *the structures described in the specification* would persuade one of skill in that the applications were in possession of molecules that actually work *in* vivo". In response, Applicants herewith submit a Declaration Under 37 C.F.R. 1.132 where results are presented showing constructs containing snRNA (U1)/anti-

HIV sequences are stable in at least three human patients 48 months post administration.

In view of the above arguments and claim amendments, Applicants assert that the rejections under 35 U.S.C. 112, first paragraph (written description) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

3. The Rejections Under 35 U.S.C. 112, First Paragraph (Enablement)

Claims 263, 284, 286-290, 292, and 296-298 are rejected under 35 U.S.C.112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing the nucleic acids in a whole organism (*in vivo*). In the Examiner's view, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims. The Action specifically states

> Applicants assert that methods were well known in the art for obtaining stable antisense and ribozyme molecule constructs and methods for their delivery into cells at the time of the priority date of the instant applications, and provide Exhibit C as evidence. However, it is noted that not one of the articles presented actually shows *in vivo* inhibition. Because the instant rejection is based on the claims encompassing *in vivo* use, applicants submission of references which fail to describe any nucleic acid-mediated inhibition *in vivo* is not convincing evidence that the claimed nucleic acids will work *in vivo.*
>
> Applicants have also submitted a number of references as exhibit D in support of the claims of enablement, However, all are at least 4 years, and most are at least 7 years past applicants effective filing date of 1995. As per M.P.E.P 2164.05 (a) the Specification Must Be Enabling as of the Filing Date.

> From the same section: The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date.

Applicants respectfully traverse the rejection. First, Applicants take issue that none of the references actually show in vivo inhibition. Specifically, two references, Vlassov et al., 1993, shows penetration of oligonucleotides into mice; Agarwal et al. shows the metabolism of phosphorothioates *in vivo*. Second, Applicants, agree that references were submitted in Exhibit D that were published after the priority date of the above-referenced application. However, Applicants respectfully point out that these references were submitted to show the utility of the claimed compositions and in response to the rejections of the utility of antisense sequences. This is permissible.

In view of the above arguments and claim amendments, Applicants assert that the rejections under 35 U.S.C. 112, first paragraph (enablement) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

4. The Rejection Under 35 U.S.C. 102

Two rejections were made. Each is discussed below.

3.1 The Rejection Over Sullenger

Claims 265, 268, 270, 272-274, 278-280, 282-284 and 288-290, and 292 are rejected under 35 U.S.C. 102 (e) as being anticipated by Sullenger et al. (U.S. Patent 5,854,038), for the same reasons of record as set forth in May 1, 2003. Specifically, it is stated

> ....Sullenger indeed discloses using snRNAs as localization tools, as evidenced from the above passage, and since furthermore, the limitation reciting two 3 stem loop structures on the snRNA is an inherent structural feature of U1 snRNA, as evidenced in figure 41 of the instant application , and the passage from applicants specification of page 43. Entities which specify cellular location include...nucleic acid species such as the snRNAs U1 and U2 which associate with cyloplasmic proteins and localize in the nucleus (Zieve and Sautereauj 1990 Biochemistry and Molecular Biology 25; I, incorporated by reference). Therefore, since the limitations newly recited in the claims are considered inherent to snRNAs, and because Sullenger clearly contemplated using snRNAs as localization tools, this recitation does not free the claims from the prior art.

Applicants respectfully traverse the rejection. First, Applicants note that an anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Foundation for Medical and Education Research,* 346 F.3d 1051, 68 USPQ2d 1373 (Fed. Cir. 2003). It is Applicants view that an enabling disclosure was not provided for the subject matter recited in amended claim 265. In particular, as argued in the previous response and as even stated in the instant Office Action, there is no explicit disclosure in Sullenger et al. regarding the nuclear localization signal containing a portion of an snRNA containing at least two loops and a reimportation signal. All that is stated is in Sullenger regarding snRNAs in the context of delivery of an agent in column 10, lines 57-58 is:

> d. Localization to nuclear compartment utilizing antigen binding site found on most snRNAs.

This is certainly not adequate. Thus, in Applicants' view, Sullenger et al. would not constitute a prior art reference and the rejection should be withdrawn.

3.2. The Rejections over Hinuma et al.

Claims 245, 249, 250 are rejected under 35 U.S.C 102 (e) as being anticipated by Hinuma et al. (U.S. Patent 6,538,107) for the same reasons of record as set forth in the Office action mailed May 1, 2003.

> Applicants point out that claim 245 has been amended to recite that the primary construct when introduced into a cell produces a secondary nucleic acid component which produces a nucleic acid product, or a tertiary nucleic acid component, or both. Applicants assert that the antisense construct of Hinuma does not actually produce a nucleic acid product or tertiary nucleic acid product. However, this is not convincing, because a broad reasonable interpretation is claim 245 is still taught by Hinuma et al. For example, claim 245 when given its broadest reasonable interpretation, provides for the same teachings as taught by Hinuma et al. For example, claim 245 claims a composition comprising a primary nucleic acid component which upon introduction into a cell produces a secondary nucleic acid product which produces a nucleic acid product. This read on any antisense oligo such as those taught by Hinuma et al., because an antisense oligo as taught by Hinuma et al could be primary nucleic acid when introduced into a cell hybridizes to its target to produce a secondary nucleic acid product (i.e. the hybridized, double standard nucleic acid) which is then cleaved by RNase H (as known to those of ordinary skill) to produce a nucleic acid product, i.e. the cleaved nucleic acid. Therefore, the newly added claim limitations still cause the claim to read on the prior art, and thus remains rejected.

First, Applicants note that as stated above, claim 245 has been amended to recite that the composition comprises **a primary nucleic acid which synthesizes a secondary nucleic acid which** syntthesizes a **gene**

product and/or tertiary nucleic acid. As noted in the previous response filed, in Hinuma et al., there is merely the teaching of the use of antisense, not transcription of a construct encoding antisense (primary nucleic acid component) to obtain a secondary nucleic acid component , the transcript and subsequent reverse transcription to a single-stranded anti-sense sequence, the nucleic acid product produced (see Figure 34). Claim 245 as amended would certainly not read on even the Examiner's interpretation of Hinuma et al. This is because claim 245 as amended recites that the primary nucleic acid synthesizes a secondary nucleic acid which synthesizes a **gene product** and/or tertiary nucleic acid. In contrast, in Hinuma, the secondary nucleic acid is actually produced by hybridization. The tertiary nucleic acid product is actually produced by degradation.

In view of the above arguments, Applicants assert that the rejections over Hinuma et al. have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

5. The Rejections Under 35 U.S.C. 103

Claims 245, 256, 257, 265, 317, 273 and 274 have been rejected under 35 U.S.C. 103 (a) as being unpatentable over Sullenger et al (U.S. Patent 5,854,038) in view of ter Meulen et al. (U.S. Patent 5,646,032), for the same reasons of record as set forth in the office action mailed May 1, 2003. The Office Action specifically states

> .....Sullenger indeed discloses using snRNAs as localization tools, as evidenced from the passage stating that is it useful to incorporate localization to nuclear compartment utilizing antigen binding site found on most snRNAs into their constructs. As pointed out above, the limitation reciting two 3 stem loop structures in the snRNA is an inherent structural feature of U1 snRNA, as evidenced in figure 41 of the instant application, and applicants

> disclosure stating that Entities which specify cellular location include:...nucleic acid species such as the snRNAs U and U2 which associate with cyloplasmic proteins and localize in the nucleus (Zieve and Sautereauj 1990 Biochemistry and Molecular Biology 25;1 incorporated by reference). This demonstrates that snRNA is a localization tool, and would thus cause reimportation. Since it inherently has two 3 stem loop structures, the limitations newly recited in the claims does not free the claims from the Sullenger as applied herein.
>
> Although applicants assert that the secondary reference, ter Meulen, would not add anything of significance, this is not considered to be convincing. Sullenger teaches antisense or decoy RNA and or DNA molecules, similar to the decoys taught by ter Muelen et al. directed against a viral replication targets. Since Sullenger taught the design of decoys generally to any viral target, and as ter Meulen et al. taught, the viral replication protein is an essential molecule for the replication of the virus, one of ordinary skill would have been motivated to target this sequence with a decoy to achieve saturation binding of the promoter and lower the rate of viral replication in the infected cell. Thus, contrary to applicants contentions, one of ordinary skill in the art would have been motivated to combine the teachings of the references, and thus, the invention is considered *prima facie* obvious in the lack of evidence to the contrary.

Applicants respectfully traverse the rejection. The PTO has the burden of establishing *prima facie* obviousness. It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fine,* 5 USPQ 2d 1596 (Fed. Cir. 1988). Once the applicant makes a showing of facts that rebuts the *prima facie*

case, the *prima facie* inference disappears. It is Applicants position that the Examiner has not satisfied this burden.

The composition of claims 245, 256, 257, 265, 317, 273 and 274 can be distinguished from Sullenger. With respect to the compositions of claims 245, 256, 257, and 317, Sullenger has not disclosed or suggested a composition comprising a primary nucleic acid which upon introduction into a eukaryotic cell produces a secondary nucleic acid which produces a gene product, or a tertiary nucleic acid , or both, in said eukaryotic cell. In the construct of Sullenger, there is merely production of a nucleic acid product from the construct in a cell. There is no teaching or suggestion of a primary nucleic acid construct which when introduced into a cell synthesizes **a secondary nucleic acid** which ultimately synthesizes a **gene** product.

With respect to claims 265, 273 and 274, as noted above, there is no suggestion or disclosure in Sullenger regarding a composition producing in addition to a sequence of interest, **a nuclear localization sequence comprising a portion of snRNA, said snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal.** There is no discussion in Sullenger regarding the secondary structure of the localization signal. Thus, one of ordinary skill in the art would not given the teachings of Sullenger consider the importance of using a nucleic acid component that would produce a portion of an snRNA containing at least two loops and a reimportation signal. It is therefore Applicants' position that the subject matter encompassed by claims 245, 246, 265, 273 and 274 would not be obvious in view of Sullenger.

The secondary reference, ter Meulen, would not add anything of significance. ter Meulen is directed to "foamy virus vectors" and is totally unrelated to the present invention.

The combination of Sullenger with ter Meulen et al. would also not be obvious, since there would be no motivation to combine these references.

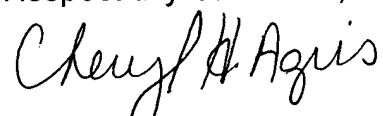
Applicants again wish to emphasize that the system of ter Meulen is totally different from that taught in Sullenger. Specifically, ter Meulen is directed to "foamy virus vectors" and expression of exogenous nucleic acids in these particular vectors. The focus of ter Meulen et al. was certainly not decoys. One of ordinary skill in the art would certainly not look to the teaching of ter Meulen with respect to decoys.

In view of the above arguments, the rejected claims are not obvious over Sullenger et al. in view of ter Meulen et al. Therefore, Applicants respectfully request that the obviousness rejection be withdrawn.

Summary and Conclusions

Claims 245-323 are pending in the above-referenced application. Claims 245, 248, 249, 251, 254, 256, 265, 268, 272, 290, 299, 303, 304-313 have been amended to more distinctly claim that which Applicants regard as their invention. Claims 246-247, 257-259, 261, 263, 266-267, 269, 271, 273-283, 314-316 have been cancelled without prejudice. If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



Cheryl H. Agris, Reg. No. 34,086

ENZO LIFE SCIENCES, INC.
c/o ENZO BIOCHEM, INC.
527 Madison Avenue, 9th Floor
New York, New York 10022
Telephone: (212) 583-0100
Facsimile: (212) 583-0150